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Polycythemia Vera in Chinese Patients: Thirty-Six Years of Experience

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Forty-one patients with polycythemia vera (PV) according to the PVSG criteria were analysed retrospectively from January 1960 to March 1996. There were 23 male and 18 female patients with a median follow-up of 66.5 months (3–431 months). Median age was 62 (range: 37–85). The median hemoglobin level at diagnosis was 18.8 g/dl. Four patients were treated by venesection alone, 20 patients received hydroxyurea and intermittent venesection, 3 were treated with radioactive phosphorus alone, and 14 had both hydroxyurea and radioactive phosphorus. During the course of illness, 14 patients (34%) developed a total of 19 thrombotic events. Of the thrombotic events, 16 were arterial and 3 were venous. Two patients had both arterial and venous thrombosis sequentially. The probability of thrombosis-free survival after treatment was 83% at 10 years and 73% at 20 years. One patient developed post-polycythemic myeloid metaplasia 24 months after diagnosis. Of 17 patients exposed to radioactive phosphorus, only 1 developed secondary acute myeloid leukemia (AML) 9 years afterwards. Of the 20 patients treated with hydroxyurea for a median duration of 63.5 months (2–130 months), there is no case of secondary malignancy. Overall survival was 83% at 10 years and 62% at 20 years. In conclusion, PV in Chinese is a relatively benign disease with a low risk of thrombosis as compared to Caucasian patients. Hydroxyurea has a very low risk of secondary leukemia and is a safe drug to use in Chinese patients with PV. Am. J. Hematol. 56:59–62, 1997.

Key Words: polycythemia vera; thrombosis-free survival; secondary AML; hydroxyurea

INTRODUCTION

Polycythemia vera (PV) is a clonal myeloproliferative disorder characterised by the increased proliferation of erythropoietic progenitors in the marrow and a raised red cell mass. The Polycythemia Vera Study Group (PVSG) formed in 1967 has proposed a set of stringent criteria that substantially strengthened diagnostic reliability [1]. Historically, untreated patients with PV had a very poor prognosis [2] with half of the patients dying within 18 months of first symptom, mostly of thrombosis. In a randomised trial, PVSG-01, in which patients were treated with phlebotomy, phlebotomy plus radioactive phosphorus (P^{32}), or phlebotomy plus chlorambucil, the beneficial effect of treatment in prolonging survival and the leukemogenic risk of chlorambucil and radioactive phosphorus were demonstrated [1]. It is a rare disease in patients with Asian or African descent [3] and most of the data on treatment were generated from western populations. We conducted a retrospective study in 41 Chinese patients with PV. This is, to our knowledge, the largest series of Chinese patients of PV reported in the English literature.

PATIENTS AND METHODS

From January 1960 to March 1996, 41 patients with PV were seen at Queen Mary Hospital, Hong Kong. The diagnosis of PV was based on PVSG criteria [1]. Red cell mass was performed in all patients with dilution of autologous red cells labelled with ^{51}Cr, according to the ICSH guidelines. The upper limits of normal are 30 and 36 ml/kg for female and male patients, respectively. Ultrasonogram computerised tomography of the abdomen and pelvis was used to exclude hepatic, renal, or uterine pathologies. Arterial O_2 saturation, vitamin B12 level,

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TABLE I. Presenting Signs and Symptoms

Signs and symptoms	N (%)
Headache	7 (17)
Dizziness	4 (10)
Tinnitis	1 (2.4)
Arterial insufficiency	
Cerebrovascular infarction	5 (12)
Intermittent claudication	1 (2.4)
Bleeding	
GI bleeding	1 (2.4)
Gum bleeding	2 (5)
Gouty arthritis	1 (2.4)
Pruritis	2 (5)
Epigastric discomfort	1 (2.4)
Plethora	22 (54)
Fundal abnormality	
Branch retinal vein occlusion	2 (5)
Congestion	1 (2.4)
Splenomegaly	28 (68)

TABLE II. Complications of PV

Complication	N (%)
Thrombotic events	19
Arterial	16
Cerebrovascular	9
Ischemic heart	5
Ischemic bowel	1
Intermittent claudication	1
Venous	3
Branch retinal vein	2
Deep vein thrombosis	1
Bleeding events	4
Upper gastrointestinal	1
Gum bleeding	2
Lower gastrointestinal	1
Myelofibrosis	1 (2.4)
Acute myeloid leukemia	1 (2.4)
Gout	6 (15)
Peptic ulcer	6 (15)
Hypertension	20 (49)

and neutrophil alkaline phosphatase (NAP) score were done by standard techniques. Treatment of the patients were aimed at reducing the hematocrit to <47%. In general, venesection was done initially to rapidly reduce the hematocrit. In occasional patients whose requirement for venesection was infrequent, venesection was used as the only treatment. Myelosuppressive therapy (chemotherapy or P^{32}) was added on with intermittent phlebotomy as necessary. Busuphan and melphalan was used in 1 and 2 patients, respectively, and were subsequently switched to hydroxyurea (initial dose 1–2 g/d), which has been used since the mid-1980s in our hospital. In patients older than 60, radioactive phosphorus (P^{32}) was used, especially before hydroxyurea was used in our hospital. Overall survival was calculated from diagnosis to time of death or date of last follow-up. Thrombosis-free survival was calculated from the treatment to the time of thrombotic event or last follow-up. Thrombotic events included both arterial and venous thrombosis. All survival curves were plotted by Kaplan-Meier method and all *P* values are 2-sided.

RESULTS

Patients and Treatments

There were 23 male and 18 female patients with a median follow-up of 66.5 months (3–431 months). Median age was 62 (range: 37–85) years. Ten of the 41 patients (24%) were below 50 years of age. The median hemoglobin level at diagnosis was 18.8 g/dl. Median hematocrit was 0.59. Median leukocyte and platelet counts were 13×10^9/l and 446×10^9/l, respectively. The presenting symptoms and signs are listed in Table I.

Four patients were treated by venesection alone, 20 patients received hydroxyurea only, 3 were treated with P^{32} alone, and 14 had both hydroxyurea and P^{32}.

Complications

Complications of the disease are listed in Table II. The major problem was that of thrombosis. During the course of illness, 14 patients (34%) developed a total of 19 thrombotic events (2 prior to diagnosis, 5 at diagnosis, 4 after diagnosis, and 4 at both diagnosis and afterwards). Two patients had both arterial and venous thrombosis sequentially. The probability of thrombosis-free survival (Fig. 1) after treatment was 83% at 10 years and 73% at 20 years.

Regarding bleeding complication, 3 had bleeding at diagnosis (2 prolonged gum bleeding and 1 bleeding duodenal ulcer) and 1 had rectal bleeding 45 months after treatment. One patient had a bleeding peptic ulcer and underwent surgery but developed cerebrovascular infarction during the post-operative period. This patient was given oral iron supplement and developed an acute inferior myocardial infarction 2 months later when diagnosis of PV was made.

One patient developed post-polycythemic myeloid metaplasia 24 months after diagnosis. Of 17 patients exposed to P^{32}, only 1 developed acute myeloid leukemia (AML) 9 years afterwards. Marrow aspirate of this patient showed dysplastic features in residual myeloid cells and cytogenetic study of the bone marrow revealed a clonal 5q-abnormality. Of the 20 patients treated with hydroxyurea for a median duration of 63.5 months (2–130 months), there is no case of secondary malignancy. There were six deaths (1 AML, 1 pneumonia, 1 chronic renal failure, 1 acute myocardial infarction, and 2 of unknown cause). Overall survival (Fig. 2) was 83% at 10 years and 62% at 20 years.

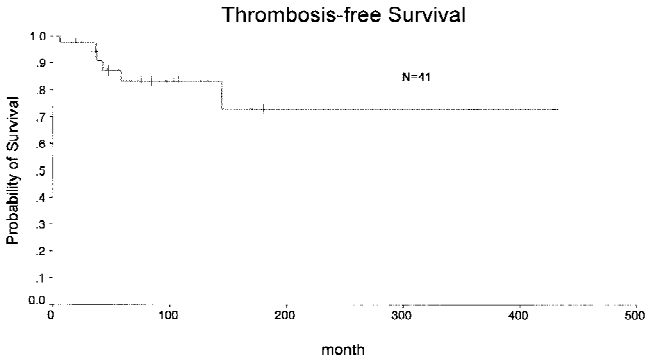

Fig. 1. Thrombosis-free survival of 41 patients with PV.

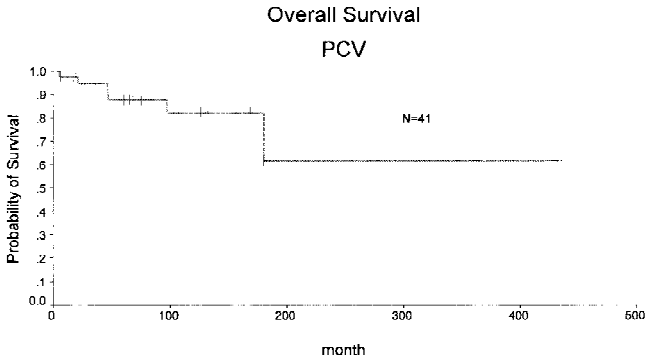

Fig. 2. Overall survival of 41 patients with PV.

DISCUSSION

PV is mainly a disease of the elderly with a mean age between 55–60 and only 20% of patients under age 50 [4]. Our study showed very similar results with the median age of 62 years and only 24% of patients were below age 50. Most of the presenting symptoms were rather non-specific but thrombohemorrhagic complications were an important presenting symptom in our patients. In one study [2], 20% of patients presented with thrombosis and more than 10% with bleeding. In contrast, in our study, 5 (12%) presented with cerebrovascular insufficiency and only 3 (7.4%) presented with bleeding.

In our patients, a total of 19 thrombotic events occurred in 34% of patients, with cerebrovascular insufficiency (N = 9, 47.4%) and cardiac ischemia (N = 5, 26.3%) accounting for more than 50% of events. This is similar to PVSG-01 trial where cerebrovascular accidents (34%) and myocardial infarction (13%) accounted for half of the thrombotic events in the first 10 years. Seven (17%) had vascular thrombosis as the presenting event (5 cerebrovascular insufficiency and 2 branch retinal vein occlusion), similar to 20% of patients having thrombotic event as the presenting symptom in one series [5]. Hepatic vein thrombosis accounted for 10% of Budd-Chiari syndrome in patients with PV in one study [6], and in another study [7] Budd-Chiari syndrome accounted for 40% of deaths in patients with PV; however, we did not encounter patients developing this complication. On the other hand, retinal vein thrombosis, uncommon in PV, constituted 10% of the thrombotic events in our patients. The thrombosis-free survival of our patients was 72% at 10 years. This compared favourably with the thrombosis-free survival of 56–62% at 10 years in the PVSG-01 trial. This may be due to a lower risk of thrombosis in Chinese in general [8,9]. In fact, the thrombosis-free survival in our patients is very similar to results in young (age <40 years) polycythemic patients in one study, 80% at 10 years [7], though the median age of our patients was 62.

Of the 17 patients exposed to P^{32}, there was one case of AML 9 years after P^{32} therapy. Radioactive phosphorus is known to be leukemogenic [10]. In the PVSG-01 study, there were 15 AML in the 156 patients treated with P^{32} after a mean of 7.3 years. This patient had clonal 5q-cytogenetic abnormality, dysplastic residual myeloid precursors in the marrow, and an aggressive clinical course, features consistent with leukemia secondary to P^{32}. In contrast, in the 20 patients treated with hydroxyurea alone, there is no case of acute leukemia after a median 63.5 months. Hydroxyurea is a non-alkylating ribonucleoside reductase inhibitor and has been found to have a low leukemogenic risk [11,12]. It is a safe and efficacious drug in the treatment of PV in our patients.

Of the 41 patients in our study, only one developed post-polycythemic myeloid metaplasia 24 months after diagnosis. In one study, this complication was more frequent and had an earlier onset in patients treated with phlebotomy alone compared with patients treated with P^{32} [13]. In our study, there were only four patients treated by phlebotomy alone while most received myelosuppressive therapy. This might account for the rarity of this complication in our study. The onset was relatively short in our patient but this might be due to the presence of subclinical disease for a variable period before diagnosis of PV was made.

The overall survival of our patients was 83% at 10 years, which was comparable to the best result of 60% at 10 years in the phlebotomy arm in the PVSG-01 trial. This was due to a low risk of thrombosis and secondary malignancy in our patients, which accounted for 29 and 23% of all deaths in their patients.

In conclusion, PV was a relatively benign disease in Chinese with a good long-term prognosis. Thrombosis remained an important complication but was less frequent as compared to the Caucasian population. Hydroxyurea is a safe agent in Chinese patients with PV. New options in the management of PV with interferon remain to be explored [14,15].

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